REMARKS

This second supplemental amendment has been prepared and filed in response to the Examiner's Interview held October 26, 2004. It is an addition or supplemental with respect to the amendment filed August 31, 2004 and the first supplemental amendment filed November 4, 2004.

Claims 32 to 38 and 45 to 51 were rejected as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729.

1. English Translation of KR 9606729

The current obviousness rejection is based on a combination of the subject matter of Voorspoels, et al, with the KR reference. A copy of the KR reference and an English translation of it have been provided with an Information Disclosure Statement filed November 19, 2004.

The following arguments are relevant to the strength of the case of *prima facie* obviousness based on a combination of Voerspoels, et al, and the disclosures in the KR reference and are in addition to the arguments in the previously filed amendments.

In addition, some additional information regarding the comparative experiments filed in the Declaration is also provided.

2. *Prima Facie* Obviousness based on a Combination of Voerspoels, et al with the KR Reference

The Voerspoels reference and the relationship of its subject matter alone to the claimed invention have been discussed in the previously filed amendments. The following additions to the argumentation in the previous amendments are based on the availability of the English translation of the KR reference.

The KR reference does disclose a general method of preparation of mucoadhesive or bioadhesive tablets for buccal administration of a drug. The method comprises spray drying a solution of a water-soluble polymer and the drug to obtain micro-pellets (claim 1). The "micropellets" were of the order of about 5 microns in size (example 1). The "micropellets" were then tabletted, as described in example 2 of the KR reference.

The polymers used in the KR spray drying method include polyacrylate, polyalginic acid and alkylcellulose polymers (claim 2). The polymer used in the KR method must be water-soluble since water is used as a solvent (see examples).

The drug included in the KR tablets is for treating local inflammation of the oral mucosa (lines 10 to 15 of the English translation). These drugs include triamcinolone and its acetonide or actetate. Tablets containing steroid hormones are neither disclosed nor suggested.

The KR reference does teach that the bioadhesive tablets produced by the spray drying method have excellent adhesion and allow sustained release of the active ingredient (page 2, lines 15 to 20 of the English translation).

However the KR reference basically teaches that the release of the active ingredient is too fast when the adhesive tablet is prepared by dry mixing instead of their method and that the spray-drying method permits an extended release of the drug molecules on page 5, lines 1 to 10. In other words, the KR reference teaches that the spray drying method produces tablets that release the active ingredient more slowly than those produced by dry mixing.

In order to combine the KR reference disclosures with those of Voerspoels, et al, to obtain the claimed invention, there must be reasonable suggestion in the art of the features that are lacking in both Voerspoels, et al, and the KR reference that are necessary to obtain the claimed invention. Also there must be reasonable motivation for one skilled in the art to combine the two references.

First, there does not appear to be sufficient motivation to combine the two references. It is true that the KR reference teaches that the bioadhesive tablets made by the spray drying method have good adhesion and better (slower) sustained release than the tablets made by dry mixing. However Voerspoels, et al, teaches that their tablets have adequate adhesion and good sustained release also.

The general conclusion in Voerspoels, et al, is that adhesion of the bioadhesive tablets made by their dry mixing method was sufficient for

maintaining testosterone plasma levels over a 24 hour period (sustained release) as shown by *in vivo* administration experiments with dogs (see last line of results in abstract). Thus one skilled in the art when presented with both prior art references would conclude that there is no reason to replace the dry mixing method of Voerspoels, et al, for making bioadhesive tablets to administer testosterone by a buccal route with the spray drying method. The spray drying method involves greater effort since equipment for spray drying must be used to prepare the pre-mix.

Thus it is respectfully submitted that one skilled in the art would find no reason to combine the references or no need to prepare tablets to administer testosterone alone to make a bioadhesive tablet containing testosterone.

Furthermore the KR references do not supply the necessary motivation or suggestion for one skilled in the art to make the bioadhesive tablet as claimed in applicants' amended claims in the supplemental amendment filed November 4, 2004. The amended claims of the supplemental amendment claim a method of making bioadhesive tablets containing either a mixture of testosterone undecanoate and testosterone or testosterone undecanoate alone.

Voerspoels, et al, teaches against including testosterone esters, especially with the higher molecular weight organic acids. First Voerspoels, et al, teaches that the bioavailability of the esters is too low, comparable with that resulting for oral administration of testosterone itself, for use in bioadhesive tablets. See the last paragraph on page 1231 and the experimental results in figs. 2 and 3. Also adhesion of the bioadhesive tablets including the decanoate ester is poor.

However applicants' experimental results in the specification in examples 1 to 5 as shown in figs. 1 to 3 show that if the bioadhesive tablets are made by spray drying with a mixture of testosterone and testosterone undecanoate, the plasma testosterone levels at the longer times, e.g. 4 hours, after administration are significantly enhanced by the presence of testosterone undecanoate and the testosterone levels are thus significantly more sustained by including the testosterone undecanoate. These results are unexpected and not suggested either by the data in Voerspoels, et al, or anything in the KR reference.

The KR reference does not disclose or suggest any information regarding the relative release rates of two different active ingredients in bioadhesive tablets made by spray drying. Applicants have shown that the relative release of testosterone undecanoate is enhanced relative to testosterone in some time ranges (e.g. around four hours) so that the testosterone levels in the plasma can be modified, e.g. to mimic the natural circadian rhythm.

The most similar ester disclosed by Voerspoels, et al, is testosterone decanoate. The release profile for this ester is shown in fig. 3d in Voerspoels, et al. Comparing this profile with the testosterone profile in fig. 2 for buccal administration of testosterone shows that the bioadhesive tablet made by including the decanoate ester with the testosterone would not have a signicantly different release profile than with testosterone alone so that there would be no purpose i.e. no suggestion, of including the deconoate or undecanoate ester with the testosterone in a bioadhesive tablet in the primary reference. There is not the slightest suggestion of this feature in the KR reference.

The applicants' results as shown in figs. 1 to 3 of the specification are therefore surprising and unexpected from these two prior art references of record. From these references one would not expect the spray drying method to enhance the relative contribution of the testosterone ester to the testosterone plasma levels resulting from buccal administration of a bioadhesive tablet containing a mixture of testosterone alone with testosterone ester as shown in fig.3 (compare figs. 1, 2 and 3 at 4 hours).

Merely because references can be combined to produce a claimed method is not enough to provide a basis for a rejection under 35 U.S.C. 103 (a). The references must provide a hint or suggestion of the modifications necessary to arrive at the claimed invention. In other words, the references must provide a suggestion of the desirability of making the particular modifications necessary to obtain the claimed invention and that suggestion is lacking here.

It is respectfully submitted that the combination of Voerspoels, et al, with the KR reference would not establish a case of *prima facie* obviousness.

3. Comparative Evidence

Applicants have provided additional information regarding the comparative experiments in the Declaration.

The solubility results reported in the Declaration are for a pre-mix that consists of only testosterone undecanoate and HPMC in the case of the sample according to the present invention and in the case of the prior art sample.

A signed copy of the Declaration showing unexpectedly superior performance for the claimed bioadhesive tablets of claim 45 and 49 (which are made by the methods of claim 32 and 36) was filed in the U.S. Patent Office per fax on October 28, 2004. If this signed copy is not available for examination, please let us know by calling the telephone number below.

The results in the signed Declaration were discussed during the interview. The Declaration reports the respective amounts of a testosterone ester, namely testosterone undecanoate, that dissolves in water at body temperature after 2 hours from tablets made by the dry mixing method of Voorspoels, et al, and by the spray-drying method according to the claimed invention. No testosterone undecanoate is present in water at body temperature when the tablet is made by the dry mixing method of Voorspoels, et al. In fact, in general the equilibrium solubilities of testosterone undecanoate would be low because of the lower solubilities of these esters in relation to testosterone itself (see column 1, page 1228, of Voorspoels, et al). However it was surprisingly found that increasing amounts of HPMC in the tablet made by the spray-drying method of the invention *promoted the solubility of testosterone undecanoate* so that a significant amount of this ester was observed to dissolve after two hours at about 0.40 % HPMC. The same solubility promoting action of HPMC is not observed when the bioadhesive tablet is made by dry mixing according to the prior art method of Voorspoels, et al. Increasing amounts of HPMC increased the amount of testosterone ester dissolved when the bioadhesive tablets were made with the amorphous premix by spray drying according to the present invention.

It should be emphasized that the solubility results in the Declaration are experimental facts and not speculative theories. The Declaration is signed by the inventor and the solubility promoting action of HPMC in the case of the bioadhesive tablet made by spray drying should be accepted as fact.

The significance of the solubility experiments reported in the Declaration is that the organic polymer (e. g. HPMC) of claims 32, 36, 45 and 49 will promote the availability of the effective ingredient, the testosterone ester, in the saliva (which is also at body temperature) when the bioadhesive tablet is made according to the spray-drying method of the present invention. Then during buccal administration a comparatively much higher super-saturation solubility of testosterone undecanoate is provided at the moist oral mucosa when the bioadhesive tablet according to the claimed invention made by spray drying is used instead of the tablet made by the prior art dry mixing method of Voerspoels, et al.

These experiments show the criticality of forming an amorphous active ingredient premix according to the claimed method instead of a mixture of crystalline testosterone ester as in the case of the prior art method.

The claim changes above have now limited the claims to a premix or tablet containing at least one testosterone ester with or without testosterone itself or to testosterone undecanoate with or without testosterone. The comparative evidence in the Declaration, which is also limited to an ester of testosterone, then supports a finding that the claimed bioadhesive tablets made by the spray drying technique with formation of an amorphous active ingredient premix are

surprisingly more effective because the bioavailability of the testosterone ester is surprisingly greater.

For the foregoing reasons and especially the comparative experimental evidence and because of the previous claim changes, withdrawal of the rejection of claims 32, 34, 35, 36, 37 and 38 and 45, 47, 48, 49, 50 and 51 as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729 (based on English CAPLUS Abstract) is respectfully requested.

4. Timpe, et al

The relationship of the disclosures in Timpe, et al, to those of the claimed invention was handled in the previously filed amendments. Briefly, Timpe, et al, would not motivate one skilled in the art to use the spray drying method to make the bioadhesive tablets with the mixture of testosterone undecanoate and testosterone.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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